Role of DC-SIGN in *Helicobacter pylori* infection of gastrointestinal epithelial cells

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1. ABSTRACT

*H. pylori* causes gastritis and increases the risk of gastric ulcer and gastric cancer. However, it was recently shown that *H. pylori* provides protection against inflammatory bowel diseases. To assess the molecular mechanism of such functions, we studied the role of DC-SIGN in *H. pylori*-infected gastrointestinal epithelial cells. DC-SIGN was found to be over-expressed in the gastric epithelial cells infected with *H. pylori* and mediated Th1 differentiation, which may be involved in *H. pylori*-induced gastric mucosal injury. In addition, DC-SIGN was also up-regulated in the intestinal epithelial cells derived from colitis mouse model, but the expression levels were blocked upon *H. pylori* infection, indicating that *H. pylori* infection may reduce both local and systemic inflammatory responses. In conclusion, we propose that gastrointestinal epithelial cells infected with *H. pylori* may lead to acquiring of immune properties via a trans-differentiation process, and regulate tissue-associated immune compartments under the control of DC-SIGN.

2. INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is one of the most common bacterial pathogens in humans, and it is closely related with gastritis, peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma. Once in contact with gastric epithelial cells, *H. pylori* causes an impairment of host immune response, which may result in gastric mucosal inflammation, injury, ulcer, and even precancerous lesions (1-3). Moreover, *H. pylori* has been found to be associated with a variety of nongastric diseases including the cardiovascular, hematological, hepatobiliary and immunological systems, among which the relationship with pathogenesis of inflammatory bowel diseases (IBDs) was given a particular attention (4,5). Epidemiological and experimental studies demonstrated a strong protective effect of *H. pylori* infection on the development of intestinal mucosal inflammation and injury, which may support the possible inverse relationship between IBDs and *H. pylori* infection (6-8). However, mechanisms behind these effects are still unknown.
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Gastrointestinal epithelial cells serve as the physical barrier, representing the first line of defense against microorganism penetration (9,10). Gastrointestinal epithelial cells also participate in the innate immune response by secreting antibacterial substances and expressing pattern recognition receptors such as Toll-like receptors (TLRs), Nod-like receptors and C-type lectins (11,12). DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin, CD209), a member of the C-type lectin superfamily, can recognize specific carbohydrate structures that are present on cell surfaces of microorganisms and target them for internalization, processing and subsequent presentation (13). Moreover, DC-SIGN can mediate DC (Dendritic cells) migration and adhesion by interacting with ICAM-2, 3 (Intercellular adhesion molecules-2, 3) (14,15). Besides adhesive and antigen-recognition properties, DC-SIGN was also demonstrated to modulate DC-mediated immune responses, especially immunoregulation of TLRs signaling (16). However, it is still unclear whether DC-SIGN is expressed on gastrointestinal epithelial cells and its role in the mucosal injury. In this study, we investigated the role of DC-SIGN in H. pylori infected gastrointestinal epithelial cells and the interventional effect of DC-SIGN monoclonal antibody named lectin-EGF antibody (17). In addition, we further used dextran sulfate sodium (DSS)-induced colitis mouse model to observe the protective effects of H. pylori on colitis.

3. MATERIALS AND METHODS

3.1. Patients and samples

A total of 72 children with chronic gastritis were recruited randomly from the department of Pediatrics of Ruijin Hospital between January 2008 and June 2009. Among them 41 were males and 31 were females with the age range from 2 to 17 years and a mean age of 10.22±3.08 years. All subjects admitted to the study were diagnosed by upper gastrointestinal endoscopy and histopathological examination without receiving antibiotics, bismuth, glucocorticoids or non-steroidal anti-inflammatory drugs during last 30 days. According to the Sydney classification system, the patients were divided into H. pylori-negative group (n = 30) and H. pylori-positive group (n = 42). Of the H. pylori-positive group, 42 patients were classified into “mild” (n = 20), “moderate” (n = 16) and “severe” (n = 6) subgroups based on the severity of chronic inflammation, or active (n = 13) and inactive (n = 29) subgroups based on the invasion of polymorphonuclear into mucosa. In addition, nine age and gender matched children without H. pylori infection and histological gastritis were enrolled as controls.

3.2. Bacteria, cells and animals

H. pylori strain (NCTC 11637; obtained from department of Microbiology of Shanghai Tong University) was grown on brain heart infusion (BHI) broth (R&D Systems) supplemented with 5% Fetal Bovine Serum (Gibco) for 36h under micro-aerophilic conditions (10% CO2, 5% O2 and 85% N2) at 37°C. H. pylori was identified by Gram stain and positive biochemical tests for urease, catalase and oxidase. For further experiments, H. pylori was collected at a concentration of 1×10^8 CFU/ml, which was measured by optical density at 600 nm.

Human gastric epithelial cells (GES-1) were cultured in RPMI 1640 medium (Gibco) supplemented with 10% Fetal Bovine Serum. After 24 h, H. pylori was added (cells:bacteria = 1:100) and co-cultured at 37°C in 5% CO2 for 12 h or 24 h. Before 2 hours of co-culture, DC-SIGN mAb was added to the cells serving as DC-SIGN mAb group. In addition, cells without H. pylori and DC-SIGN mAb were grown for control.

DSS-induced colitis mouse model was used in this study (18). Female specific pathogen free BALB/c mice (aged 6-8 weeks, weight 16-20g, purchased from the Experimental Animal Co. Lake Hayes) were randomly classified into control group (n= 10), DSS group (n= 10) and H. pylori+DSS group (n= 10). Control group was fed with sterile saline-solution. DSS group was treated with 5% DSS solution as drinking water for 7 days. H. pylori+DSS group was gavaged with 1×10^8CFU/ml of H. pylori suspended in 500 µl BHI broth for 3 days. The mice were then fed with normal diet for 4 weeks before 7 days of 5% DSS.

3.3. Immunohistochemistry

The paraffin sections of human gastric tissues and mouse intestinal tissues were processed by de-waxing, hydration and blocking of non-specific binding sites. The sections were incubated with 1:100 primary antibody at 4°C overnight and 1:400 secondary antibody for 30 min at room temperature. Antibodies used were as follows: mouse anti-human DC-SIGN mAb (R&D Systems) and biotinylated anti-mouse IgG (Invitrogen) for human gastric tissues, rat anti-mouse DC-SIGN mAb (eBioscience) and biotinylated anti-rat IgG (Invitrogen) for mouse intestinal tissues. After washed with PBS, sections were subsequently incubated with 1:400 streptavidin-peroxidase for 30 min at room temperature. Finally, sections were treated with staining, dehydration, mounting and examination under a light microscope (Olympus). PBS, instead of primary antibody, was used as negative control and a known positive section was used as positive control.

The cell membrane or cytoplasm of epithelial cells stained with a distinct brown orange coloration represents positive cells (19). Immunohistochemistry (IHC) scores were calculated by multiplying the percentage of positive cells (0 is <10% positive cells, 1 is 10%-30% positive cells, 2 is 31%-50% positive cells, 3 is 51%-75% positive cells and 4 is > 75% positive cells) by stain intensity (0 is no staining, 1 is weak staining, 2 is moderate staining and 3 is strong staining) in five different high power fields for each section. Only the IHC scores of a tissue more than 4 were assigned to the positive group.

3.4. Histology and histological score assessment of colitis

Paraffin-embedded distal colonic sections from the mice were prepared in 5 mm thicknesses. Sections were stained with hematoxylin/eosin (HE) to assess histological changes by Zeiss Axioplan 2 imaging microscope equipped with an AxioCam MRc5 camera (Carl Zeiss). Histological scoring was ranked according to the amount of inflammation, depth of inflammation and the amount of crypt damage (20)
Figure 1. The expression of DC-SIGN on gastric epithelial cells of patients with chronic gastritis. A, Periodic acid-Schiff (PAS) staining of gastric tissues (final magnification ×200). a: control; b: mild chronic gastritis; c: moderate chronic gastritis; d: severe chronic gastritis. B, The coexpression of DC-SIGN and Cytokeratin 8 in gastric epithelial cells of patients with chronic gastritis (×200). a: DC-SIGN; b: Cytokeratin 8; c: Merge. Green indicates DC-SIGN positive cells; Red represents Cytokeratin 8 positive cells; Yellow represents DC-SIGN positive and Cytokeratin 8 positive cells.

3.5. Double staining immunofluorescence

The paraffin embedded sections of human gastric tissues were processed with baking, dewaxing, hydration and fixation. The sections were incubated with 1:100 mouse anti-human DC-SIGN mAb (R&D Systems) and rabbit anti-human Cytokeratin 8 mAb (Bioworld) at 4°C overnight, followed by incubation with 1:200 FITC labelled anti-mouse IgG (Invitrogen) and RPE labelled anti-rabbit IgG (Invitrogen) for 1h at room temperature, and finally observed under multifunctional automated fluorescence microscopy (Carl Zeiss).

3.6. Flow cytometry

Human gastric epithelial cells, mouse intestinal epithelial cells and mouse spleen cells were harvested and transferred to 6-well cell culture plate at 10^5 cells/well followed by incubation with fluorescein-labelled DC-SIGN mAb, MHC II mAb and CD86 mAb for 30 min at 4°C. Phenotypic analysis was performed by flow cytometry using a FACS Calibur (BD FACS Aria™ Cell Sorter).

Mouse splenic cells with a concentration of 1×10^6 cells/ml were stained with FITC-labelled CD4 mAb (eBioscience) for 30 min at 4°C, then fixed and permeabilised, and again stained with 1:100 APC- labelled IFN-γ mAb (eBioscience) and PE-labelled IL-4 mAb (eBioscience). Flow cytometry was performed on a FACS Calibur.

3.7. Quantitative real-time PCR assays

Total RNA was extracted from the human gastric epithelial cells using Trizol Reagent kit (Invitrogen), and cDNA was synthesized using the Reverse Transcription kit (Promega). DC-SIGN primer sequences, sense 5′-ATTTCTCAACTCTATTCAAGCC-3′, antisense 5′-TCTCACAGAAAAGGGGAGACAC-3′, and the length of amplified products was 283bp. The GAPDH as an inner conference, sense 5′-GAGTCAGAAGGTTGACTGTC GTAT-3′, antisense 5′-AGTCTTCCTGGGTGCACTGAT-3′, and the length of amplified products was 521 bp. PCR amplification was performed using SYBR Green PCR master mix kit.

3.8. ELISA

CD4+ T cells were isolated from the peripheral blood of healthy volunteers by density gradient centrifugation and magnetic beads. The obtained cells (3×10^6 cells/ml) were then co-cultured with H. pylori infected gastric epithelial cells (3×10^6 cells/ml) in a 96-well plate for 5 days. Cell culture supernatants were collected and levels of IFN-γ and IL-4 were determined by ELISA (Biosource).

3.9. Statistical analysis

The database analysis was performed by SPSS software, version 16.0. Measurement data were represented as mean ± SD and measured using one-way analysis of variance (ANOVA) and t test. Enumeration data was evaluated by chi-squared test and Fisher's exact test. The relationship between two sets of data was analyzed using Spearman coefficients. A value of P < 0.05 was considered significant.

4. RESULTS

4.1. DC-SIGN expression in human gastric mucosa tissues

DC-SIGN was rarely detected in normal human gastric mucosa tissues, but the positive rate increased significantly in gastric mucosa tissues of patients with chronic gastritis, especially in the epithelial cells and the stroma (Figure 1 A). The expression of DC-SIGN in the H. pylori-positive group (71.43% [30/42]) was significantly higher than the H. pylori-negative group (30% [9/30]), suggesting that the expression of DC-SIGN was correlated with H. pylori infection (r = 0.410, P < 0.01). In addition, the expression of DC-SIGN in the H. pylori infected gastric epithelial cells was increased according to the severity of chronic inflammation. Compared to the mild subgroup (50% [10/20]), the moderate subgroup (87.50% [14/16], P < 0.01) and severe subgroup (100% [6/6], P < 0.01), implying that the expression of DC-SIGN was correlated with the degree of chronic inflammation in the H. pylori-positive group (r = 0.330, P < 0.01). Furthermore, the expression of DC-SIGN in the active subgroup (84.62% [11/13]) was also higher than the inactive subgroup (65.52% [19/29], P > 0.05). However, there was no
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Figure 2. *H. pylori* infection promotes DC-SIGN expression on human gastric epithelial cells. A, The expression of DC-SIGN, CD80 and CD86 on human gastric epithelial cells. Gastric epithelial cells were transferred to a 6-well plate at a density of $2 \times 10^5$ per well, then treated with *H. pylori* or/and DC-SIGN mAb, and subsequently incubated with FITC-labelled DC-SIGN mAb (eBioscience), PE-labelled CD80 mAb (eBioscience) and APC-labelled CD86 mAb (eBioscience), respectively. B, The expression of DC-SIGN on *H. pylori* infected gastric epithelial cells at mRNA levels. DC-SIGN mRNA expression was determined for 0, 0.5 and 2 h after *H. pylori* infection by RT-PCR. Data are representative of more than three independent experiments. ** represents $P < 0.01$.

significant difference between groups ($r = 0.195, P > 0.05$).

4.2. H. pylori infection promotes DC-SIGN expression on human gastric epithelial cells

Expression of DC-SIGN and its co-stimulatory molecules CD80 and CD86 were relative low on human gastric epithelial cells in normal culture condition, but increased significantly at 12hours after being treated with *H. pylori* and reached peak levels at 24hr (Figure 2A). In addition, the level of DC-SIGN mRNA increased significantly at 2 hr (Figure 2B). Treatment with DC-SIGN mAb not only inhibited the expression of DC-SIGN in *H. pylori*-infected human gastric epithelial cells, but also decreased the expression of co-stimulatory molecules
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4.3. H. pylori infected gastric epithelial cells induce a Th1-dominated cytokine response

IFN-γ and IL-4 were measured to determine differentiation towards a Th1 (T help cell 1) or Th2 (T help cell 1) phenotype. IFN-γ is termed a Th1 phenotype, while IL-4 can drive differentiation to a Th2 phenotype. The cytokines of IFN-γ and IL-4 were detected in the cocultured supernatants from gastric epithelial cells and CD4+ T cells. Compared to H. pylori 0hr group, the IFN-γ levels (P < 0.01) and IFN-γ /IL-4 ratio (P < 0.01) were increased in the H. pylori 12hr and the 24hr groups while downregulated when treated with DC-SIGN mAb (Figure 3). However, no changes were observed on IL-4 secretion (P > 0.05). This suggests that DC-SIGN mAb may reduce the H. pylori-induced Th1 response.

4.4. Characterization of DSS-induced colitis in mice

HE staining (∗×200) revealed higher neutrophils infiltration of the intestinal tissue in DSS group and H. pylori+DSS group versus control (Figure 4A). Disease activity index (DAI) defined as weight loss, stool form and stool blood, was used to evaluate the protective effect of H. pylori against colitis (21). Compared to controls (0.6±0.55), disease activity was significantly up-regulated in the DSS group (10.8±0.65, P < 0.01) and the H. pylori+DSS group (6.9±0.87, P < 0.01) (Figure 4B). In addition, histological scores of intestine biopsies were also elevated in the DSS group (7.0±1.77, P < 0.01) and the H. pylori+DSS group (5.1±0.75, P < 0.01) versus control (0.7±0.24) (Figure 4C). Importantly, disease activity and histological scores were improved in the DSS-induced mice by treatment with H. pylori (P < 0.05), suggesting that H. pylori infection may reduce some inflammation (Figure 4B, C).

4.5. H. pylori infection reduces DC-SIGN expression on both intestinal epithelial cells and splenic CD11c (+) dendritic cells from DSS-induced colitis mouse model

DC-SIGN was rarely detected in normal

Figure 3. Gastric epithelial cells-induced Th1 and Th2 cytokine secretion. Isolated CD4+ T cells (3×10^5 cells /ml) were cocultured with gastric epithelial cells (3×10^4 cells/ml) infected with H. pylori for 12h or 24h (cells:bacteria = 1:100). Before 2 hours of coculture, DC-SIGN mAb was added to the cells serving as DC-SIGN mAb group. At last, coculture supernatants were collected and tested for cytokines of IFN-γ (A), IL-4 (B) and IFN-γ / IL-4 (C). ∗ represents P < 0.05, ** represents P < 0.01.
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Figure 4. Histology (A), disease activity index (B), and histological score (C) in mice with DSS-induced colitis. a: control; b: DSS group; c: H. pylori+DSS group. H. pylori infection can significantly ameliorate the DSS-induced colitis * represents $P < 0.05$, ** represents $P < 0.01$.

...intestinal tissues, but significantly increased in the intestinal tissues of DSS group and H. pylori+DSS group, especially in the epithelial cells and stroma (Figure 5A). The expression of DC-SIGN was more obvious in DSS group than in H. pylori+DSS group and was correlated with DAI ($r = 0.330$, $P < 0.01$).

Flow cytometric analysis revealed that mouse intestinal epithelial cells and splenic CD11c (+) dendritic cells from controls exhibited lower expression of DC-SIGN, MHC-II and CD86 compared with those from the DSS group and the H. pylori+DSS group. Among them, the DSS group had the highest expression levels (Figure 5B, C). This suggests that H. pylori infection can inhibit DC-SIGN, MHC-II and CD86 expression on mouse intestinal epithelial cells and splenic CD11c (+) dendritic cells.

4.6. H. pylori infection ameliorates a Th2-dominated cytokine response in DSS-induced colitis mouse model

Compared to controls, IL-4 expression levels of mouse splenic CD4+ T cells were increased in the H. pylori+DSS group, and peaked in the DSS group. No significant changes of IFN-γ were detected among those groups (Figure 6). This showed that H. pylori infection could down-regulate IL-4 expression of splenic CD4+ T cells and thus ameliorate the Th2 response in DSS-induced colitis mouse.

5. DISCUSSION

H. pylori colonizes the human gastric mucosa and causes inflammation and immune response in human. Despite a vigorous innate and adaptive immune response to H. pylori, the bacterium persists for the lifetime of the host (22). During its long co-existence with the host, H. pylori may have evolved to maintain a bacterium/host dynamic equilibrium, and imbalance of which may be pivotal for the development of diseases (12,22). Thus, understanding the mechanisms of immune responses in host is very important for the development of new strategies against H. pylori-induced gastric diseases.

Many studies about the innate immune responses to H. pylori in epithelial cells have centered on TLR4 (23,24). However, H. pylori lipopolysaccharide (LPS) even with high concentrations was not effectively recognized by TLR4 in gastric epithelial cells lines (25). In addition, TLRs localized on the basolateral poles of epithelial cells reduced the likelihood for H. pylori to be recognized by these receptors (26). Recently, it was demonstrated that H. pylori can interact with DC-SIGN to modulate the host immune response (26,27). Here, we show that the expression of DC-SIGN on gastric epithelial cells increased in chronic gastritis, and its expression level was correlated with H. pylori infection and the degree of gastric mucosal inflammation. The expression of DC-SIGN as well as CD80 and CD86, were also increased on GES-1 cells after treated with H. pylori in vitro and can be significantly decreased by DC-SIGN mAb. Furthermore, GES-1 cells produce higher levels of IFN-γ and IFN-γ/IL-4 after H. pylori infection, which can also be inhibited by DC-SIGN mAb treatment. This suggests that H. pylori infection induces a Th1-predominant host immune response in the gastric mucosa, while DC-SIGN mAb intervention may...
Figure 5. Expression of DC-SIGN, MHC-II and CD86 on mouse intestinal epithelial cells and splenic CD11c (+) dendritic cells. a: control; b: DSS group; c: H. pylori+DSS group. A, Immunohistochemical staining of mouse intestinal tissues (SP ×200). B, Expression of DC-SIGN, MHC-II and CD86 on mouse intestinal epithelial cells. Intestinal epithelial cells (5×10^5 cells/ml) isolated by flow cytometry and cell sorting were incubated with FITC labelled-DC-SIGN mAb (eBioscience), MHC II mAb (eBioscience) and CD86 mAb (eBioscience); C, Expression of DC-SIGN, MHC-II and CD86 on splenic CD11c (+) dendritic cells. Isolated splenic cells (5×10^5 cells/ml) were incubated with PE labelled-CD11c mAb (eBioscience) and further stained with FITC labelled-DC-SIGN mAb, MHC II mAb and CD86 mAb respectively.
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Figure 6. IL-4 and INF-γ expression levels in mouse splenic CD4+T cells. Isolated mouse splenic cells (1×10^5 cells/ml) were incubated with FITC-labelled CD4 mAb and again stained with APC-labelled IFN-γ mAb and PE-labelled IL-4 mAb.

play a key role in maintaining the Th1/Th2 equilibrium.

As outlined above, our study has showed that H. pylori infected gastric epithelial cells could express DC phenotypes, such as DC-SIGN, CD80 and CD86, which are rarely detectable in the normal cells. We further demonstrated that H. pylori-infected gastric epithelial cells can stimulate CD4+ T cells to secrete IFN-γ. On the basis of these observations, we propose that gastric epithelial cells infected by H. pylori may experience a trans-differentiation process termed “Epithelial Immune Cell-like Transition”, leading to acquisition of immune properties. Trans-differentiation is a biological process where one cell type committed to a particular specialization switches into another cell type, involved in morphological, phenotypic, and functional changes such as epithelial-mesenchymal transition (EMT) (28). H. pylori infection can not only stimulate the recruitment and activation of DCs but also induce gastric epithelial cells to exert antigen-presenting function via trans-differentiation, thus participating in gastric mucosal injury. However, DCs are involved in H. pylori immune escape (2), while H. pylori infected gastric epithelial cells induce Th1 responses, which may be associated with the regulation of immune compartments. Further study will be needed to clarify the interaction of gastric epithelial cells and DCs in a micro-inflammatory state of H. pylori-associated gastrointestinal diseases, and the role of DC-SIGN in regulating gastric epithelial cell trans-differentiation.

Some studies have reported that H. pylori infection appears to protect against IBD, but the underlying mechanisms are unknown (6,7). Luther et al have demonstrated that H. pylori DNA exhibits a high ratio of immunoregulation to immunostimulatory sequences and has the ability to reduce pro-inflammatory responses from DCs (8). In this study we use DSS-induced colitis mouse model to investigate the relationship between H. pylori infection and IBD. Our previous study has demonstrated that DC-SIGN could be expressed on intestinal epithelial cells in mice with colitis and further mediates a Th2 response (29). In the current study, we found that DC-SIGN, MHC II and CD86 were all expressed on intestinal epithelial cells in the early stage of colitis, and their expression levels were significantly correlated with the degree of disease activity and intestinal pathological injury. However, H. pylori infection inhibited their expressions and improved the intestinal mucosal injury, indicating that H. pylori may attenuate the T cell response mediated by intestinal epithelial cells. In addition, H. pylori infection could decrease the expressions of DC-SIGN, MHC II and CD86 on splenic CD11c (+) DCs and down-regulate IL-4 levels in splenic CD4+ T cells. These results suggested that H. pylori can relieve the local and systemic inflammatory response in DSS-induced mouse colitis mainly by regulation of DC-SIGN expression. However, further investigation into the protective mechanisms by H. pylori, such as how DC-SIGN interacts with T cells and its subsequent changes in cytokines, are needed.

In summary, we demonstrated that the increased expression of DC-SIGN on gastrointestinal epithelial cells plays a key role in H. pylori infection-associated gastrointestinal diseases through two biological phenomena: trans-differentiation and regulation of immune compartments.

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7. REFERENCES


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Abbreviations: H. pylori: Helicobacter pylori; IBDs: inflammatory bowel diseases; TLRs: Toll-like receptors; DC-SIGN: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; DC: Dendritic cells; ICAM-2, 3: Intercellular adhesion molecules-2, 3; mAb: monoclonal antibody; DSS: dextran sulfate sodium; BHI: brain heart infusion; Th1: T help cell 1; Th2: T help cell 2; HE: hematoxylin/eosin; IHC: Immunohistochemistry; ANOVA: one-way analysis of variance; PAS: Periodic acid-Schiff; DAI: disease activity index; LPS: lipopolysaccharide; EMT: epithelial-mesenchymal transformation

Key Words: H. pylori, C-type lectin, DC-SIGN, epithelial cells, trans-differentiation

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